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ORIGINAL ARTICLE

CT Evaluation of Cholangiocarcinoma and its Correlation with Endoscopic Retrograde Cholangiopancreaticography

Shalini Goel*, Apar Mathur, Juhi Agrawal**, Pankaj Kumar Nitharwal***, RajatSinghal**, Mukesh Mittal******

ABSTRACT

Introduction: Cholangiocarcinoma (CC) is the most frequent malignant tumour of the biliary tract, accounting for 10-20% of all primary liver tumours. It may occur at any segment of the bile duct, i.e. from the terminal ductules to the ampulla of Vater. Therefore, CC tumours are differentiated in intrahepatic (iCC) and extrahepatic (eCC) tumour and the iCC is subdivided into peripheral and perihilar CC (pCC), the latter also being called Klatskintumour. Various imaging modalities are available to accurately diagnose cholangiocarcinoma such as imaging modalities including contrast enhanced Computed tomography (CT) of abdomen in triple phase and MRCP which is a non-contrast MR technique in which the T2-weighted contrast between bile (long T2) and adjacent tissues (short T2) is accentuated by using heavily T2-weighted sequences, and other invasive modalities in endoscopic retrograde cholangiopancreaticography (ERCP), which is retrograde injection of contrast agent into the biliary tract allows the assessment of localization and morphology of bile duct strictures. Out of these currently ERCP is considered gold standard for hilar patency.

Aims and objective: To determine accuracy of hilar patency as assessed by CECT with gold standard of ERCP.

Materials and methods: In this prospective study, 50 consecutively registered patients (24 women, 26 men; mean age, 55 years; range, 34-81 years) with clinical / sonographic suspicion of cholangiocarcinoma were examined between May 2017 to May 2019 in tertiary care hospital. All patients were scheduled to undergo triple phase computed tomography (TPCT) based on the patient's reports and symptoms. Following TPCT, ERCP was done in indicated patients.

Inclusion and exclusion criteria: Adult patients of either sex who were clinically / sonographically suspected cases of cholangiocarcinoma referred by gastroenterology/ gastro surgery department were included in the study.

Patients with history of allergy to iodinated contrast agent, and those with renal insufficiency (serum creatinine concentration > 1.5 mg/dL) were excluded.

Sample size: A sample size of 50 adult patients of either sex was taken referred to us by gastroenterologist/ gastro surgeons suspected of having cholangiocarcinoma.

Conclusion: The diagnostic accuracy of CECT is comparable to the gold standard ERCP in the evaluation of hilar patency.

INTRODUCTION

Cholangiocarcinoma (CC) is the most common malignancy of the biliary tract and it account for 10-20% of all primary liver tumors. Most (95%) of CC are adenocarcinomas with a high proportion of fibrous stroma. Despite recent advances in patient care, surgical resection of the tumor remains the only potentially curable therapy, leading to a 5-year survival of 30-35%. CC may occur at intrahepatic (iCC) or extrahepatic (eCC) (27-42%) locations; the iCC is subdivided into peripheral (6-8%) and perihilar CC (pCC) (50-67%), the later also being called Klatskin tumor. The etiology of CC is not fully understood, but several risk factors like primary sclerosing cholangitis (PSC), liver fluke infestations (Opisthorchis viverrini, Clonorchissinensis),

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hepatolithiasis, Thorotrast exposure, and choledochal cysts have been identified. The Liver Cancer Study Group of Japan classified iCC into three types based on the dominating morphologic feature: mass-forming (the most common), periductal infiltrating, and intraductal growth. Growth pattern of eCC is classified as sclerosing, nodular and papillary. Imaging modalities like ultrasound, computed tomography, magnetic resonance imaging, and also positron emission tomography/computer tomography are useful in the diagnosis, primary staging, and restaging of CC[1]. Computed tomography (CT) is a commonly used approach for the detection and staging of cholangiocarcinoma. In the arterial phase of CT scan, arterial anatomy of the liver and surrounding structures can be visualized which aids in planning of surgery. In the portal venous phase, CC mainly show incomplete rim-like contrast enhancement at the tumor periphery and low intratumoural attenuation, increasing the precision in estimating the tumor size and the detection of satellite nodules. In late-phase scans (5-10 min after contrast injection), a late enhancement of the tumor can be observed, representing the amount of fibrous stroma. In case of tumor necrosis and/or mucin-containing cells, the delayed enhancement may disappear. CT scan helps indiagnosis of dilated bile duct, assessment of liver parenchyma, vascular encasement, lymph node, and metastasis. Additionally, CT is useful for detecting the presence of liver atrophy. Dilatation of bile ducts combined with atrophy suggests the obstruction of the portal vein[2]. In endoscopic retrograde cholangiopancreaticography (ERCP), retrograde injection of contrast agent into the biliary tract allows the assessment of localization and morphology of bile duct strictures. On the findings of asymmetric, irregular strictures malignancy is suggested. Moreover, resectability can be evaluated. Compared to non-invasive imaging techniques, ERCP allows tissue collection for cytological and histological investigation, allows biliary stent implantation as palliative treatment in irresectable tumors or as a preoperative procedure prior to definitive/ curative surgery. ERCP would also be helpful in definitive diagnosis of primary sclerosing cholangitis which is a major risk factor for development of CCA. ERCP has evolved from a diagnostic procedure into a primarily therapeutic procedure for a variety of biliary and pancreatic disorders[3].ERCP is associated with a risk of infection known as, ascending cholangitis thought to be related to instrumentation of poorly draining, obstructed bile ducts.

In addition to FDA-mandated post-marketing surveillance of duodenoscope high-level disinfection guidelines from each manufacturer, proposed solutions to address duodenoscope contamination have included a culture and quarantine process following disinfection and before reuse, ethylene oxide gas sterilization, and a call for disruptive technology, including disposable single-use duodenoscopes and redesigned forceps elevator mechanisms. Human factors must also be considered as a potential contributor. Instruments that have not undergone adequate manual disinfection can still harbour living bacteria, even after gas sterilization with ethylene oxide[4].

Despite the threats and challenges as detailed, abundant opportunities exist for novel ERCP applications. Duodenoscope-assisted cholangiopancreatoscopy has evolved to single-operator platform with high-resolution imaging capabilities that can support a range of intraductal applications, from direct visualization and targeted sampling of intraductal neoplasm, to lithotripsy of bile duct and pancreatic duct stones. Therapeutic intervention for chronic pancreatitis, including stent placement and/or treatment of pancreaticolithiasis, the later often supported by either pancreatoscopy-targeted intraductal lithotripsy or extracorporeal shockwave lithotripsy, represent a potential area of expanded opportunity for ERCP[5]. The use of Self Expandable Metallic Stent (SEMS) for treatment of benign bile duct strictures, including those related to cholecystectomy, liver transplant, and chronic pancreatitis, is associated with high technical and clinical success rates and requires fewer ERCPs per patient to achieve stricture resolution compared with use of plastic stents[6]. Addition of photodynamic therapy to biliary stent therapy may prolong overall survival compared with biliary stent therapy alone and may prolong metal stent patency in patients with unresectable cholangiocarcinoma[7].

AIMS AND OBJECTIVE

To determine accuracy of hilar patency in cholangiocarcinomaas assessed by CECT with gold standard of ERCP.

MATERIALS AND METHODS

The study protocol was approved by the institutional research review board, and informed consent was obtained from all patients. In this prospective study, 50 consecutively registered patients (24 women, 26 men; mean age, 55 years; range, 34-81 years) with clinical / sonographic suspicion of cholangiocarcinoma were examined between May 2017 to May 2019. All patients were scheduled to undergo triple phase computed tomography based on the patient's reports and symptoms. Following TPCT, ERCP was done in indicated patients.

STUDY DESIGN

It is a type of descriptive cross- sectional study.

STUDY LOCATION

This study was conducted in the department of Radio-diagnosis, G.I.P.M.E.R, New Delhi in association with the department of Gastroenterology, G.I.P.M.E.R., New Delhi

STUDY DURATION

The study was conducted for two years from June 2017 to May 2019.

INCLUSION AND EXCLUSION CRITERIA

Adult patients of either sex who were clinically / sonographically suspected cases of cholangiocarcinoma referred by gastroenterology/ gastro surgery department were included.

Patients with history of allergy to iodinated contrast agent, and those with renal insufficiency (serum creatinine concentration > 1.5 mg/dL) were excluded.

SAMPLE SIZE

A sample size of 50 adult patients of either sex was taken referred to us by gastroenterologist/ gastro surgeons suspected of having cholangiocarcinoma.

METHODOLOGY

COMPUTED TOMOGRAPHY IMAGING TECHNIQUE-

The complete CT study was explained to each subject with risk involved during and / or after intravenous contrast administration and radiation exposure during the CT study and written and informed consent was taken. Renal function tests were checked before intravenous contrast administration.

Image acquisition was carried out abide by ALARA (As Low as Reasonably Achievable) principle, which required careful patient preparation and scanning technique. Scans were performed in a cephalic to caudal direction, during shallow inspiration breath hold with scan range from lung bases to the pubic symphysis.

CT parameters used tube voltage 100 kVp, tube current 150 mAs, 1ml/kg of non-ionic contrast agent (350mg of iodine/ml) was injected at the rate of 5ml/s through an 18G intravenous antecubital cannula.

For cholangiocarcinoma, triple phase contrast study was done with following phases:

1. Pre-contrast CT
2. Late arterial phase CT performed 20–30 seconds after contrast medium injection.
3. Hepatic venous phase CT is performed 25–30 seconds after the completion of late arterial phase scanning.
4. Delayed phase scanning (performed 150–180 seconds after the completion of hepatic venous phase scanning)

Evaluation

Acquired data was evaluated in axial, coronal, and sagittal sections and with various post processing methods to look for, site / size / type / margins of lesion, CBD, CHD and IHBR dilatation, enhancement pattern, vascular infiltration, lymph nodes involvement, metastatic lesions and hilar patency.

Radiological diagnosis was made based on above mentioned findings. Histopathological correlation was done to evaluate the efficacy of CT in diagnosis of cholangiocarcinoma. ERCP was performed after CT evaluation to look for hilum patency in indicated patients. Final diagnosis was made with histo-pathological evaluation and ERCP for hilar patency

STATISTICAL METHODS

The collected data was entered in excel sheet and analysed using SPSS-20 version. Statistical analysis of acquired data is done by calculating the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of TPCT in diagnosing and staging cholangiocarcinoma. TPCT was correlated with ERCP for hilar patency. Quantitative data was expressed as mean, standard deviation and difference between groups was tested by student's t-test. Nonparametric test like Mann Whitney 'U' test were used if required. While qualitative data was expressed in percentage. Difference between proportions was tested by chi-square test or fisher's exact test. 'P' value less than 0.05 was considered statistically significant.

OBSERVATION

50 patients were included in the study. Out of 50, 45 (90%) patients had one lesion. only 3 (6%) patients had 2 lesions and 2 (4%) patients had multiple lesions. (Table-1). Out of 50, 45 patients (90%) had lesion having irregular margins. only 1 patient (2 %) had lesion having polypoidal margins and 4 (8%) patients had smooth surface lesion. (Table-2). Out of 50 patients, 32 patients (64%) had lesion showing irregular peripheral enhancement with gradual centripetal enhancement. Lesion showing heterogeneous enhancement was noted in 14 patients (28%), homogenous enhancement of wall thickening is noted in 3 patients (6 %) and homogenous enhancement of lesion is noted in 1 patient (2 %) (Table-3). Out of 50 patients, CBD is dilated in 20 patients (40 %). CBD is not dilated in 30 (60 %) patients (Table-4)

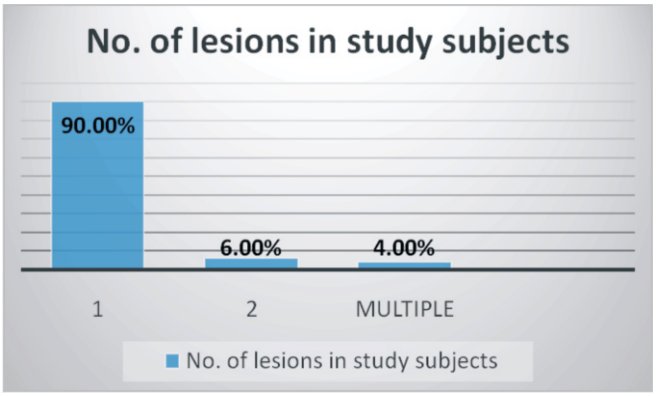
Out of 50 patients on TPCT, hilum was patent in 25 patients (50%) and was not infiltrated by the lesion. Hilum was infiltrated by the lesion in another 25 patients (50%). ERCP was done in 43 patients and hilum was patent in 21 patients and was not patent in 22 patients (Table-5)

Table 1: Hilar patency on CT/ERCP

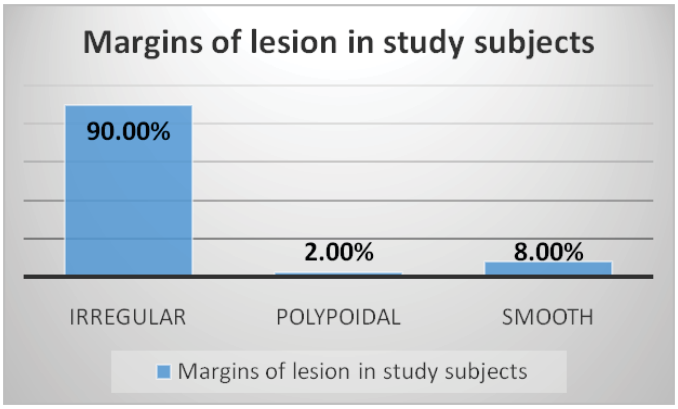
No. of lesions	No.	%
1	45	90
2	3	6
Multiple	2	4

Table 2: Margins of lesion in study subjects

Margins of lesion	No.	%
Irregular	45	90.0
Polypoidal	1	2.0
Smooth	4	8.0



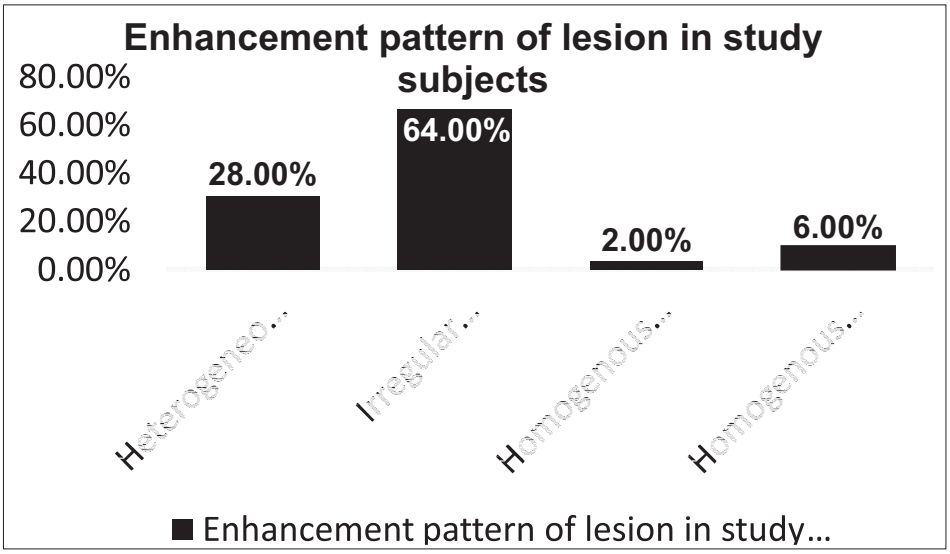
Bar chart showing distribution of number of lesions in patients



Bar chart showing distribution of lesion margins in patients

Table 3: Enhancement pattern of lesion in study subjects

Enhancement pattern of lesion	No.	%
Heterogeneous enhancement	14	28.0
Irregular peripheral enhancement with gradual centripetal enhancement	32	64.0
Homogenously enhancement	1	2.0
Homogenously arterial enhancement of wall thickening	3	6.0



Bar chart showing enhancement pattern of lesion in patients

Table 4: CBD status

CBD status	No.	%
Dilated	20	40.0
Non-dilated	30	60.0

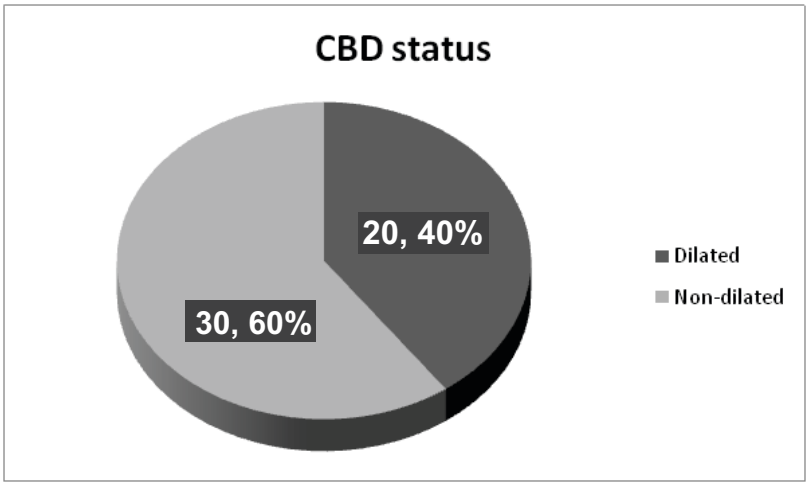
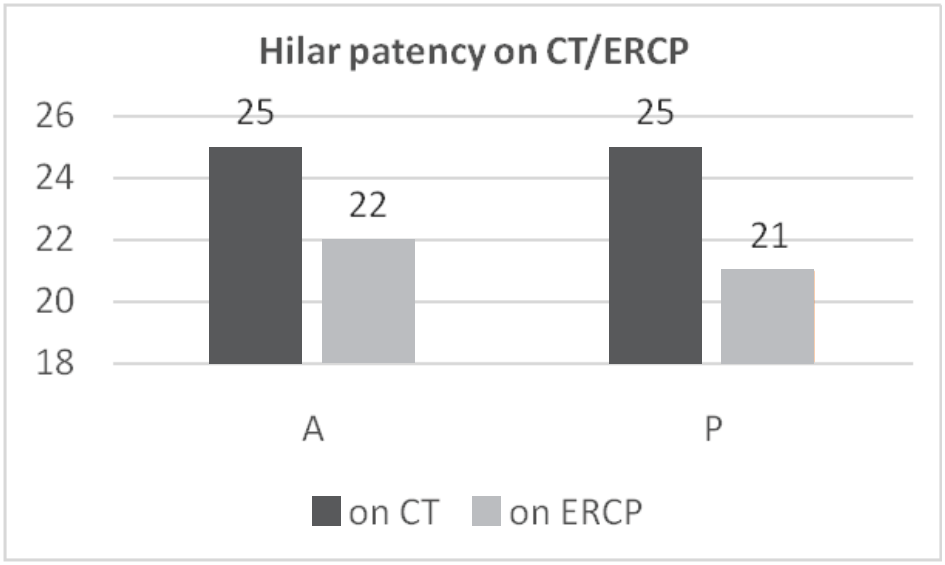


Table 5: Hilar patency on CT/ERCP

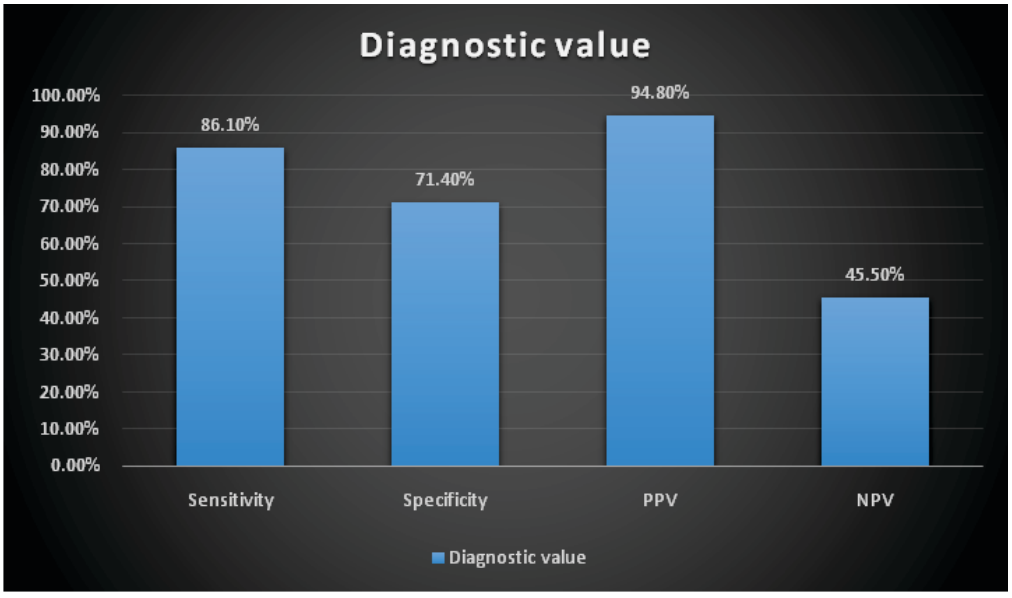
Hilar Patency	CT (n=50)	ERCP (n=43)
A	25	22
P	25	21



Bar graph showing comparison of hilar patency on CT and ERCP

Table 6: Diagnostic accuracy of radiological part

Diagnostic value	% (95% CI)
Sensitivity	86.1 (72.1-94.7)
Specificity	71.4 (29.1-96.3)
PPV	94.8 (85.1-98.4)
NPV	45.5 (25.7-66.7)
Accuracy	84.0 (72.9-92.8)



Bar graph showingdiagnostic accuracy of CT in evaluating cholangiocarcinoma in study subjects

RESULT

In this study by CT, hilum was patent and was not infiltrated by the lesion in 25 patients (50%) out of 50 patients while hilum was infiltrated by the lesion in another 25 patients (50%).

ERCP was done in 43 patients and hilum was patent in 21 patients and was not patent in 22 patients.

Based on results, sensitivity of CT in diagnosing CCA is 86.1 %, specificity is 71.4 %, PPV is 94.8 %, NPV is 45.5% and accuracy is 84% (Table-6)

For long, ERCP was the standard established procedure for evaluation of patients with obstructive jaundice. Due to recent advances in MDCT technology permitting faster acquisition in a single breath hold and upgraded software techniques for image reconstruction, MDCT is now more sensitive for determining the preliminary level and cause of obstruction. Due to sub-second acquisition and multiphasic approach, newer studies have further refined the role of MDCT in terms of specific diagnosis and staging of the pathology. So, multiphasic, single breath hold,sub centimetreiso-voxel scanning with post processing through volume acquisition, maximum intensity projections (MIPs), and multiplanar reformations (MPR) all help to increase the diagnostic accuracy, which is immensely helpful in

1. a) Differentiating benign from malignant stricture.
2. b) Staging complicated biliary malignancies in terms of involvement of biliary confluence, invasion, and encasement of the adjacent major arterial and venous channel making it inoperable, as well as regional lymphadenopathy and hepatic metastasis.

Hence, Multiphasic MDCT of the abdomen with pancreatic and venous phase through the hepato-biliary-pancreatic region is now the accepted worldwide protocol for pancreatico-biliary malignancies.

CONCLUSION

The results of this study showed the diagnostic accuracy of CECT is comparable to the gold standard ERCP in the evaluation of hilar patency in cholangiocarcinoma.

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REVIEW ARTICLE

Research Impact & Metrics

Monica Jain*, Shivankan Kakkar, Dhirendra Kumar Mahawar****

INTRODUCTION

Medical research can offer both solutions for existing problems and modification in the current treatment guidelines. It can impact either a limited group of patients or the whole population. In other words, research impact is the link between research outputs and public health[1].

Research should not just sit on a shelf doing nothing but collecting dust, instead it should be thoughtfully published[2]. The research should get disseminated to a wide range of health care stakeholders who have influence in areas where it can actually enact change. The patient subset must be considered when designing research outputs so as to ensure that the findings are accessible and that they can be widely used as a tool for change.

Being an Academician and a Researcher

From a practical point of view, medical scientists while working on any study are always under great pressure for time and resources. Designing a protocol where they will be able to participate and learn is, therefore, of the utmost importance[3].

Lessons learned are a key part of any research work. One should use lessons of the past to inform the future wherever possible as it can act as a catalyst for a research study set up, while also offering information on what hasn't worked previously. That doesn't mean a research team has to follow lessons learned, but it's sensible to consider them.

In the present context, there should be a coexistence of traditional academic activities with research. It's about adding to what already exists, and not substitution.

There is a need to encourage academics and researchers to think in more detail about impact from the inception of a study, and who will be affected by the findings, the research has far more of a coherent arc throughout the study and the consideration of impact has a tangible effect on the researchers' focus throughout.

Disseminating Your Research Work

Dissemination involves the publication and discovery of academic research. It can be thought of as a niche group interested in academics talking about a common topic and sharing knowledge.

However, we are living in a digital era with online open access[4]. A digital identity is a set of validated digital attributes and credentials for the digital world, similar to a person's identity for the real world. Additionally, there are various online open access repositories (**Figshare**, being the most prominent one) where researchers can preserve and share their research outputs in a citable, shareable and discoverable manner[5].

Figure 1:- Adapted from Benefits of Open Access by Danny Kingsley and Sarah Brown, http://aoasg.org.au/. CC-BY

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The adjoining figure demonstrates benefits of an online open access system and how it works. It basically involves a dissemination between or within the academic and or research field of specific industries or topics for the purpose of collecting, verifying, understanding, and or sharing information that can be used to broaden knowledge and understanding of a topic or principle or other aspect of interest[6].

Research Publication Metrics

The capacity to assess the impact of research publications is a growing area of significance, particularly for the purposes of applying to secure financing and partaking in career progression. Understanding how research is assessed can also assist one to identify impactful journals to publish with. It is essential to take note that research publication metrics do not supplant other measures of excellence such as peer review - however stand close by as a more extensive measure of impact[7].

Metrics can be of either **Bibliometrics or Altmetrics**. Bibliometrics provides a quantitative analysis of the impact of research. It takes into account the number of citations for individual articles to look for how they would have impacted on the research arena. It stands side by side with the other qualitative measures of excellence such as peer review[8].

Bibliometrics

- **Authors and Institutions:** This includes publication and citation counts, also known as the *h-index*. It was originally proposed by Mr. J. E. Hirsch in the year 2005, and since then it has gained a great popularity among researchers however bibliometics scholars have also proposed a few variants (i.e., *g-index* and *m-index*).
- **Journals:** Many of the journal level metrics are based on ranking journals. This is in turn based on the number of citations. Examples include the Journal Impact Factor (i.e., citations over a period of preceding two years) and CiteScore (i.e., citations that are divided by publications over a period of preceding four years).

Finding Out Your *h-index*

Here, we would like to elaborate on *h-index* since it is the best author level metric in scientific research. The *h-index* attempts to measure the impact of the published work of a researcher. Itis the maximum value *h* such that *h* articles have minimum *h* citations each. For example, if an author has six publications, with 10, 9, 6, 4, 3 and 2 citations (in descending order of citations), then the author's *h-index* is 4, because the author has four publications with 4 or more citations.

There are a number of resources where an author's *h-index* can be found out, however the value of the *h-index* can differ depending upon the resource. For example, the *h-index* calculated from Google Scholar tends to be more than that from Web of Science and or SCOPUS. From the Web of Science, an author can find out *h-index* for all his/her publications. Search is done by entering either the author's name or his/her ORCID or ResearcherID. Whereas, SCOPUS has an author summary page containing *h-index* along with all other author information. Google Scholar is another great resource for finding out the *h-index,* however it requires you to create a Google Scholar profile before providing the *h-index* and other metrics[9].

Altmetrics

Altmetrics is a type of non-conventional bibliometrics which is designed to complement other measures such as citation counts, impact factors etc[10]. Measures in altmetrics include:

- **View Counts:** includes page hits and PDF downloads.
- **Discussions:** includes blogs, comments and wikipedia citations. This also includes social media activities especially on Twitter, YouTube and Facebook.
- **Saves:** includes tools like CiteULike, Mendeley etc.

As is the case with the conventional bibliometrics, there is no common approach to what measures are the best for calculating altmetrics. Although, these measures are highly controversial and debated- with some arguing for their use while others arguing against them. It is necessary to note here that the bibliometric or altmetric scores alone cannot effectively evaluate scholarly works[11].

CONCLUSION

Research impact is to improve and or change the current practices. Moreover, it allows us to identify strategic and key factors that help us to manage the health care challenges effectively.

Research outputs should be widely distributed. Using a consistent form of name and author IDs (ORCID and or ResearcherID), mentioning institutional affiliations, promoting one's research in social media (Twitter, Facebook, YouTube), self-citations as well and platforms (Figshare) for sharing research outputs are certain suggestions for a better research impact and in return, the individual author's profile including the *h-index* would be raised.

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DRUG UPDATE

Tirzepatide

Monica Jain*, Shivankan Kakkar, Om Prakash Choudhary*****

INTRODUCTION

Tirzepatide (also called as 'twincretin') is the first-in-class and only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist, which can significantly reduce glycemic levels and improve insulin sensitivity, and decrease body weight by more than 20%.[1] Tirzepatide (Proprietary Name- Mounjaro of Eli Lilly and Company) has been recently approved by the Food and Drug Administration (FDA) for use in the United States of America (USA). The approved indication of Tirzepatide being to normalize blood glucose levels in adult patients with Type II Diabetes Mellitus (DM) in addition to diet and exercise. Several clinical trials are underway that have also shown initial prospects for the use of Tirzepatidein Obesity control in Type II DM patients.

Type II DM is the most common form of diabetes, a chronic and progressive condition in which the body does not make or use insulin normally, leading to high levels of glucose in the blood. Despite the availability of a number of medications to treat diabetes, many patients do not achieve the recommended blood glucose goals. Three different doses of tirzepatide (5 milligrams, 10 milligrams and 15 milligrams) were evaluated in a total of five clinical trials as either a stand-alone therapy or as an add-on to other diabetic medicines. Patients that were randomized to receive the maximum recommended dose of tirzepatide (15 milligrams) had lowering of their hemoglobin A1c (HbA1c) level by 1.6% more than placebo when used as stand-alone therapy and 1.5% more than placebo when used in combination with a long-acting insulin. In trials comparing tirzepatide to other diabetes medications, patients who received the maximum recommended dose of tirzepatide had lowering of their HbA1c by 0.5% more than semaglutide, 0.9% more than insulin degludec and 1.0% more than insulin glargine. Obesity was common among study participants, with an average body mass index of 32 to 34 kg/sqm reported. Among patients randomized to the maximum recommended dose, the average weight loss with tirzepatide was 15 pounds more than placebo when neither were used with insulin and 23 pounds more than placebo when both were used with insulin. The average weight loss with the maximum dose of tirzepatide was 12 pounds more than semaglutide, 29 pounds more than insulin degludec and 27 pounds more than insulin glargine. It was also seen that those patients receiving insulin without tirzepatide tended to gain weight.

Chemical Structure

Tirzepatideis a linear peptide,$C_{225}H_{348}N_{48}O_{68}$ which contains 39 amino acid, size is same as GIP and GLP-1. It is trade name is Mounjaro and other brand names are LY3298176, GIP/GLP-1 RA.It belongs to the secretin family related hormones of gut peptides. The starting amino acid sequence is the same as human GIP and it retains 9 homologous AAs from this peptide 10 AAs shared by GIP and GLP-1 as well. 4 AAs correspond of GLP-1 molecule at same position, and 10 amino-terminal are identical to the sequence of exendin-4 (a lizard salivary peptide known as Helodermasuspectum),also called exenatide.

Mechanism of Action

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist for the treatment of Type II DM and also lowering blood glucose levels. It is also used for long standing Type II DM to achieve normal glucose levels. Tirzepatide stimulates cAMP generation in combination of GIP and GLP-1 in pancreatic ß-cells.Tirzepatide is an acylated

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peptide engineered to activate the GIP and GLP-1 receptors[1]. insulin secretion which expressed in regions of the brain it regulate food intake.Tirzepatide at 5–15 mg per week reduces both HbA1c (1.24 to 2.58%) and weight (5.4–11.7 kg) which is not done by any other single drug.

Dosing, Efficacy and Safety

Start with a 2.5 mg dose, which is not intended for glycemic control. After 4 weeks,we can increase 5 mg injected subcutaneously once weekly. If more glycemic control is needed, add 2.5 mg increments after a minimum 4 weeks. In continuous glucose monitoring (CGM) to compare the 24 hr glucose profile for participants given tirzepatide compared with those given insulin degludec,[2,3] if was found that, the treatment with tirzepatide is superior glycemic control measured as Once-weekly using CGM compared with insulin degludec in participants with Type II DM on metformin, with or without a SGLT2 inhibitor. These data provide additional evidence to the effect of tirzepatide and potential for achieving glycemic targets without increase of hypoglycaemic risk compared with a basal insulin[4]. A dose-dependent superiority on glycemic efficacy and decrease weight is evident with tirzepatide vs placebo, GLP-1 RAs and basal insulin. Tirzepatide did not increase the odds of hypoglycaemia but was associated with increased gastrointestinal adverse events.

In efficacy and safety of tirzepatide versus titrated insulin degludec in Type II DM controlled by metformin with or without SGLT2 inhibitors,in patients with Type II DM, tirzepatide (5, 10, and 15 mg) is superior to titrated insulin degludec, with markedly decrease in HbA1c and bodyweight at week 52 and a less risk of hypoglycaemia. Both Tirzepatide and GLP-1 receptor agonists shows similar safety profile.Theglycaemic efficacy of GIP/GLP-1 receptor agonist tirzepatide in Type II DM results from concurrent improvements in diabetes pathophysiology, namely β-cell function, insulin sensitivity, and glucagon secretion. These effects were large and help to explain glucose-lowering ability. It is glucose dependent insulinotropic polypeptide.

Other GLP-1 receptor agonist drugs include: Dulaglutide (Trulicity) (weekly), Exenatide extended release (Bydureonbcise) (weekly),Exenatide (Byetta) (twice daily),Semaglutide (Ozempic) (weekly), Liraglutide (Victoza, Saxenda) (daily).

Adverse Effects

Nausea, vomiting, diarrhoea, constipation, decreased appetite, upper abdominal discomfort and abdominal pain are the common adverse effects to the use of tirzepatide. It can result in a substantial weight loss as well. Pharmacologically, signaling studies demonstrate that tirzepatide mimics the actions of native GIP at the GIP receptor but shows bias at the GLP-1 receptor to favor cAMP generation over β-arrestin recruitment, weaker ability to drive GLP-1 receptor compared to GLP-1.

Clinical Development

Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether Tirzepatide causes such tumors, including medullary thyroid cancer, in humans. Tirzepatide should not be used in patients with a personal or family history of medullary thyroid cancer or in patients with type MEN syndrome. Tirzepatide has not been studied in patients with a history of pancreas inflammation (pancreatitis), and it is not indicated for use in patients with type 1 diabetes.Tirzepatide received priority review designation for this indication.

Tirzepatide works like two hormones that help people feel full after eating[5]. At those doses, tirzepatide achieved a reduction of A1C of f 2.09% and a weight loss of 7.8 kg (17 lbs). In contrast, semaglutide(Ozempic) posted a drop of 1.86% in A1C and 6.2 kg (14 lbs) in body weight[6]. It's not yet approved for weight loss, but doctors can prescribe. One of the most popular existing weight loss drugs, called semaglutide, originated as a diabetes medication,was FDA-approved to treat obesity in 2021[7]. In the SURPASS-2 study, all doses of tirzepatide were superior to semaglutide 1 mg, a selective GLP-1 RA, in both HbA1c and body weight change from baseline at week 40 in patients with Type II DM, taking metformin with HbA1c more than target value. The overall safety profile of tirzepatide is equal to semaglutide[8]. Both tirzepatide and dulaglutide are GLP-1-type drugs indicated for the treatment ofType II DM,, but they work in slightly different ways.The efficacy and safety of once-weekly tirzepatide as compared with semaglutide, a selective GLP-1 receptor agonist, are unknown. Semaglutide and tirzepatide, the two molecules do not act in precisely the same way. Semaglutide is a GLP-1 analogue whereas tirzepatide is a GIP/GLP-1 agonist. Both are prone to gastrointestinal side-effects. Injection of tirzepatide at 15 mg for the same duration lowered the body weight by 13.1% in surpass-2 with an ETD of 6.4% compared to semaglutide 1 mg treatment. Use of tirzepatide other than diabetes-Eli Lilly's (NYSE:LLY)

tirzepatide has demonstrated a significant weight loss benefit in individuals without diabetes in a late-stage trial. Insulinotropic effect is glucose-dependent insulinotropic peptide that stimulates the release of insulin from the beta cells in the pancreas in order to maintain low blood sugar levels after eating. It also increases the production of these cells and reduces the rate at which they break down.

CONCLUSION

Type II DM and Obesity are illnesses that have no particular cure so far, although, can be kept under control by proper treatment and integrating lifestyle adjustments. The disturbing increase in the number of Type II DM patients with obesity in recent years, requires new medical advancements in order to improve administration, reduce dosing, and simultaneously address multiple comorbidities with a single medication. Tirzepatide offers a novel and better alternative in this regard. However, additional clinical trials on a larger subset of population are required to ascertain its efficacy and safety.

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CASE REPORT

Recurrent Calcifying Fibrous Tumour in Axilla: A Rare Case Report

Deepika Hemrajani*, Prachi Gupta, Tarushi Gupta*****

INTRODUCTION

Calcifying fibrous tumour is a rare benign lesion. Calcifying fibrous tumor (CFT), synonymous with a calcifying fibrous pseudotumor, is a rare, distinct tumor-like soft tissue lesion that usually affects children and young adults, with in their subcutaneous and deeps of tissues of extremities, trunk, neck and scrotum[1,2].

Calcifying fibrous tumor (CFT), originally defined by Rosenthal and Abdul-Karim (1) as a childhood fibrous tumor with psammoma bodies, was subsequently renamed by Fetsch et al(2)as a calcifying fibrous pseudo tumor. It has tendency of non destructive local recurrence. Histologically, it is characterised by a non-encapsulated, well-circumscribed mass, containing dense hyalinised collagen, bland spindle cells, lymphoplasmacytic infiltrate sand psammoma bodies, or diastrophic calcifications.(3)

CASE REPORT

A 7 year-old child presented with slow growing swelling over left axilla. Patient was operated for similar swelling 4 years back. Clinical examination revealed a firm, well defined mobile non tender swelling of size 8x5 cm in left axilla. The patient's complete blood count and other routine bio-chemical values were within normal limits. There was no family history. MRI scan revealed multiple altered signal intensity masses in left axillary region, few of them are conglomerated to each other with internal hypo intensities. Excisional biopsy was performed and sent for histopathological examination.

Grossly three grey white to grey brown well circumscribed, lobulated firm soft tissue masses of size 8x8x3.5, second 6.5x4.5x3.5 and smallest was of 2x1.5x1cm were present. External surface of all masses was capsulated globular grey white. Cut surface of all was fibrous grey white.

Microscopically sections show presence of loose hyalinized bands of collagen, hypocellular in nature, along with areas of dystrophic calcification,presence of lymphoid follicles with germinal centres and large number of reactive plasma cells favouring calcifying fibrous pseudotumour.

DISCUSSION

Calcifying fibrous tumor (CFT) is a rarely seen entity that usually occurs in children and young adults, with a slight increase in risk in women. Clinically, it appears as a slow growing, non tender mass.

These lesions were originally described as arising in the sub cutaneous and deep soft tissues, mostly in the extremities and the neck areas[2] but more recently CFT have been found to be ubiquitous.

Most lesions are solitary but multi focal lesions are also reported specially arising from pleura and peritoneum and uncommonly in mesentry[4,5]. Malignant transformation has not been reported[6].

A few were thought to evolve from inflammatory myofibroblastic tumor(IMT), but larger studies failed to confirm this and ultra structural studies revealed fibroblastic features[4,7]. However, in the literature, there are cases that maybe related to trauma and Castleman's disease[8-12].

Nascimen to et al have observed local recurrences in 3 of 10 patients in his study[13]. Ultra structural studies show that calcifications occur as a result of cytoplasmic degeneration in the fibroblasts[10,13]. The local recurrence rate for CFT has been estimated to be approximately 10%. the rate of recurrence in gastrointestinal CFTs as opposed to CFTs arising at other sites remains unclear. Some authors have suggested that gastric CFTs, for example, have no tendency for local recurrence compared to soft tissue CFTs[14].

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The his to pathological features of CFTs are generally easily recognizable from other reactive or benignneo plastic lesions. Inflammatory myofibroblastic tumor (IMT), Plexi form fibromyxoma, reactive nodular fibrous pseudo tumor(RNFP), nodularfasciitis, desmoidfibromatosis, giant cell fibroma, desmoplastic fibroblastoma, fibroma of tendon sheathand calcifying aponeurotic fibroma might be considered in the differential diagnosis. Amyloid fibromas show positive staining with Congo red[15].

There are few studies regarding cytogenetic abnormalities in calcifying fibrous tumors. By using fluorescent in situhybridization, Hoffmann et al attempted to detect trisomy 7 and trisomy 8 which has been reported in other benign fibrous tumors. Due to the low signal intensity, they were not able to complete the study[16]

In another study, Fukunaga et al found that CFT had a diploid DNA contentby flow cytometry[17]. Whether CFT is a true neoplasm or are active process still remains unknown[16-18]. Future molecular studies can be helpful for detecting the biologicbehavior of CFT.

Further studies are needed to clarify the recurrence rate of CFTs in different anatomic sites. Such studies could drive guidelines for management of patients with CFT. In summary, CFT is a rare soft tissue neoplasms and conservative excision is sufficient to cure the patient. However, local recurrence can be seen in some cases. Thus clinical follow up is important. These lesions may be identified more often in the future due to increased awareness and technical advances in diagnosis.

Fig 1: Gross Specimen

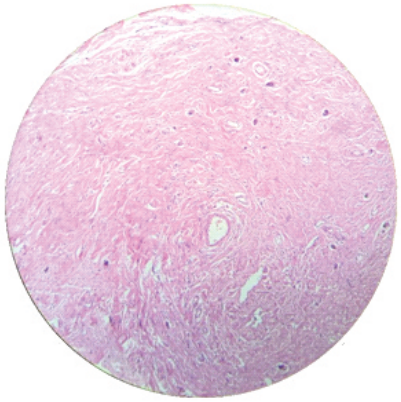

Fig 2: 4x

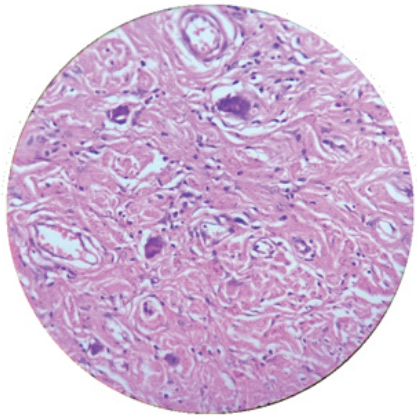

Fig 3: 40x

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CASE REPORT

Prenatal Diagnosis of Ebstein's anomaly using Spatio-temporal image correlation (STIC) technique.

Mukesh Mittal*, Pankaj K Nitharwal, Abhinav Mathur***, Bajrang Lal Bishnoi******

ABSTRACT

Ebstein's anomaly is a congenital heart disease. Cause of this anomaly is failure of delamination of the tricuspid valve which results in apical displacement of septal and posterior leaflets of tricuspid valve. The valve is abnormal in position and in morphology. It is usually thickened and incompetent leading to tricuspid regurgitation and tricuspid stenosis to a lesser extent. The prognosis of this anomaly is poor and it results in fetal hydrops followed by fetal demise in majority of the cases. Antenatal diagnosis of this can be made by bidimensional echocardiography.Recently, the technological breakthrough of three-dimensional ultrasound (3D-US) offered new diagnostic tools for congenital heart defects, less dependent on the operator experience, when compared to two- dimensional ultrasound (2D-US). The spatio-temporal image correlation (STIC) technique is a new technique and by this we can acquire the fetal heart volume and its structures as a 4D cineloop sequence showing the complete cardiac cycle.

Purpose : To describe the features of Ebstein's anomaly through 2D and 3D ultrasonography with STIC Technique.

Material And Methods: Studied the ultrasonographic features of prenatally diagnosed Ebstein's anomaly using Philips Affinity 70 G Ultrasound Machine at Zenana Hospital, SMS Medical College, Jaipur. A convex volumetric transducer (4–8 MHZ) was used. The heart volume was acquired using Spatio-temporal image correlation (STIC) application. The fetal thorax was identified in a transverse plane showing the four cardiac chambers (four-chamber view). The region of interest (ROI) was set to contain the fetal heart and its vascular connections. The acquisition angle was defined at 25° and the capture time was set to 12.5 sec. After volume acquisition, the heart was analyzed in rendering mode, in static planes, and in cine loop sequences. Cardiac anatomy was assessed by thick slice method on a sagittal plane showing the valves.

INTRODUCTION

Congenital heart defects (CHDs) are the most common type of birth defect and are a leading cause of birth-defect associated morbidity and mortality[1]. The prevalence of CHDs is approximately 80 per 1000 live births[2]. Ebstein's anomaly is a type of CHD characterized by a malformation of the tricuspid valve and the right side of the heart[3]. Ebstein's is a rare CHD, accounting for less than 1% of all CHDs, with an estimated prevalence of approximately 0.5 per 10 000 live births[1].

A variety of cardiac abnormalities are associated with Ebstein's anomaly, including atrial septal defect, conduction system abnormalities, patent foramen ovale, pulmonary stenosis or atresia, and ventricular septal defect[1].

Echocardiography is the diagnostic test of choice to definitively diagnose Ebstein's anomaly. However, other modalities such as chest radiograph, electrocardiogram (ECG), and prenatal sonography are often the initial tests to detect the cardiac abnormality, leading to further evaluation.

Bidimensional ultrasound (2D-US) is the technique of choice for congenital heart defects screening, but it presents some limitations such as an operator-dependent exam, fetal position, oligohydramnios, real-time exam, and time-consuming image acquisition. Three-dimensional ultrasound (3D-US) depends less on the operator when used to evaluate the fetal heart. After the volume acquisition, the heart can

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be analyzed in multiple planes, some of which cannot be obtained using 2D-US[4].

The Spatio-temporal image correlation (STIC) technique allows the acquisition of the fetal heart volume and its structures, and the visualization in the multiplanar mode or as a 4D cine loop sequence showing the complete cardiac cycle[5,6].

CASE:-A 24-year-old woman (G2P1A0) had come for a routine antenatal check-up with 6-month amenorrhea. She was otherwise asymptomatic. No history of maternal diabetes or any drug intake by patient. There was no significant family history of congenital heart disease.

USG FINDINGS:- The grayscale ultrasound examination revealed fetal cardiomegaly. The right atrium was found to be abnormally enlarged with the apical displacement of the posterior and septal leaflet. Colour Doppler examination revealed the presence of tricuspid regurgitation and TR jet arising from the middle of the right ventricle. The tricuspid valve leaflet was displaced caudally into the right ventricle. There is atrialization of the right ventricle and the functional right ventricle is small. The left side of the heart is compressed and small in size. The left ventricular outflow tract was normal.

DISCUSSION

In 1866, Wilhelm Ebstein described the autopsy

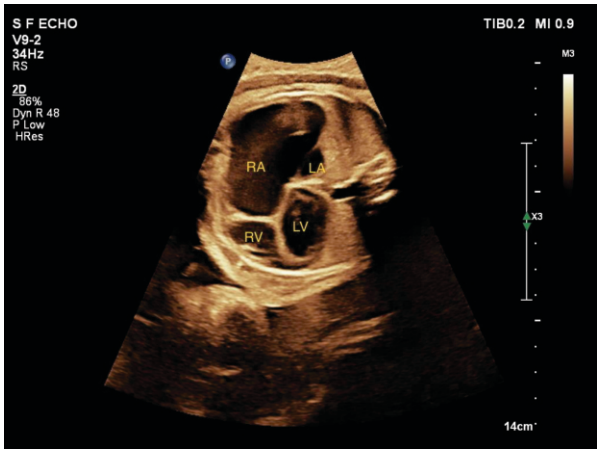

Image A- 2D echocardiography findings in a 24-week fetus with Ebstein's anomaly. Enlargement of the RA and displacement of the tricuspid valve with a small right ventricle. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle.

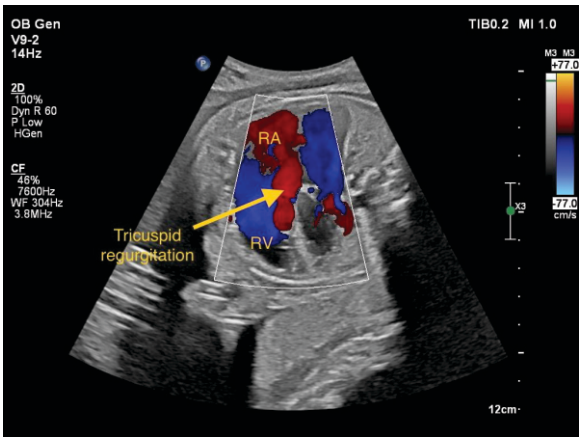

Image B -Colour Doppler showing jet of blood across the tricuspid valve during ventricular systole.

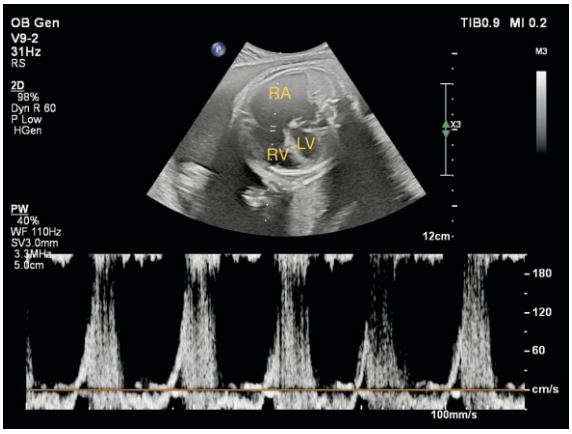

Image C- Showing increased velocity across the tricuspid valve of about 180 cm/sec.

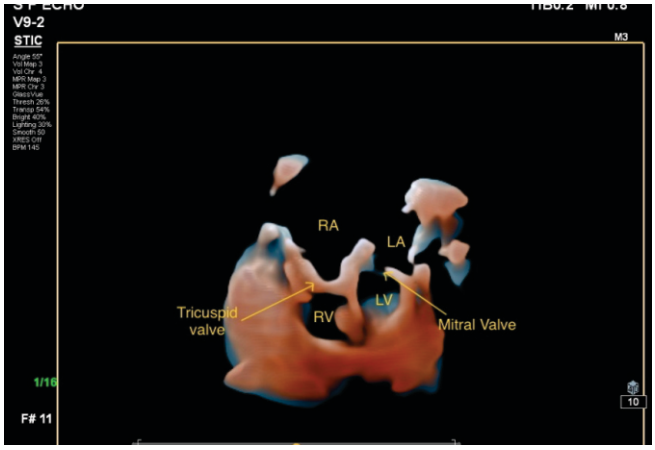

Image D- STIC rendering mode in a 24-week fetus with Ebstein's anomaly. The RA is enlarged and the tricuspid valve is displaced caudally with a shortening of the RV. STIC Spatio-temporal image correlation, RA right atrium, RV right ventricle.

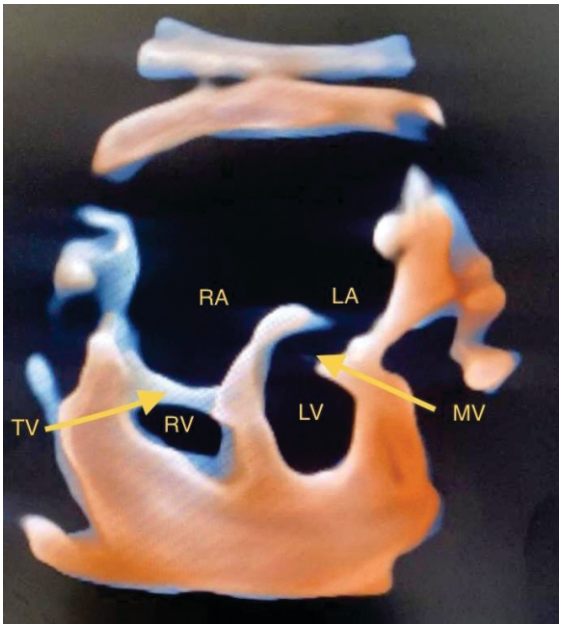

Image E- Showing the large right atrium (RA) and the small right ventricle (RV) are demonstrated in addition to the displaced attachment of the tricuspid (TV) in comparison to the mitral valves (MV).

findings of the tricuspid valve and right ventricle of a 19-year-old labourer who had had a history of cyanosis and dyspnoea since childhood[7].

Ebstein's anomaly develops during the first weeks of intrauterine life as the tricuspid valve fails to develop normally. During week 7, the atrioventricular valve leaflets begin to develop from the myocardial tissue of the ventricles by a process called delamination. By the end of week 12, the tricuspid valve is fully formed. In a normal heart, the tricuspid valve has three leaflets: anterior, posterior, and septal[8].

Ebstein's anomaly is a malformation of the tricuspid valve and right ventricle characterized by-

(1) Adherence of the septal and posterior leaflets to the underlying myocardium (failure of delamination, namely, splitting of the tissue by detachment of the inner layer during embryologic development);

(2) Downward (apical) displacement of the functional annulus (septal > posterior > anterior);

(3) Dilation of the "atrialized" portion of the right ventricle, with various degrees of hypertrophy and thinning of the wall;

(4) Redundancy, fenestrations, and tethering of the anterior leaflet; and

(5) Dilation of the right atrioventricular junction (true tricuspid annulus)[9].

The spectrum of malformation in Ebstein's anomaly may range from only minimal displacement of the septal and posterior leaflets to an imperforate membrane or muscular shelf between the inlet and the trabecular zones of the right ventricle. Many patients with Ebstein's anomaly have other structural cardiac anomalies and abnormalities of the cardiac conduction system, such as atrial septal defect, patent foramen ovale, pulmonary stenosis or atresia, and ventricular septal defects[10].

Most cases of Ebstein's anomaly are sporadic and the exact mechanism for the anomaly is not entirely understood. Case-control studies suggest genetic, reproductive, and environmental risk factors; for example, the anomaly is more common in twins, those with a family history of congenital heart disease, and those with maternal exposure to benzodiazepines. There is also a weak link between maternal lithium therapy and the presence of Ebstein's anomaly, although this rarely occurs[9].

Bidimensional echocardiography is the gold standard for the antenatal diagnosis of Ebstein's anomaly. The key findings are enlargement of the right atrium, dysplastic tricuspid valve with caudal implantation, tricuspid insufficiency, and atrial septal defects. Functional pulmonary atresia with confluent pulmonary truncus and arteries with an inverted blood flow is also frequent[6].

Spatio-temporal image correlation (STIC) is an advance in four-dimensional ultrasound, where the spatial and temporal information are combined to generate a dynamic volume of the fetal heart that can be analyzed in multiplanar mode or rendered planes. STIC allows the acquisition of a complete cardiac cycle in a dynamic volume shown as a cine loop sequence.

The ideal plane for capture is a transverse view of the fetal thorax (four-chamber view). During the second trimester, captured angles between 20° and 25° are sufficient to include the whole heart and its connections. Acquisition time varies from 7.5 to 15.0 sec, depending on the chosen angle and resolution[11,12].

In our case, the diagnosis was confirmed by bidimensional echocardiography. We tested the spatial motion covered by three-dimensional ultrasound. Enlargement of the right atrium and the displacement of

the tricuspid valve is clearly seen by the STIC technique. We used the thick slice method, considered the standard technique to evaluate the valve leaflets. Lower implantation of the tricuspid valve was clearly seen.

We suggest that the association of these new techniques with bidimensional echocardiography will increase the diagnostic test sensitivity for congenital heart defects during prenatal care.

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